The pending claims are listed in the attached: Appendix A2 [Pending claims (clean copy)].

REMARKS

The status of the claims is as follows:

Amended:	1,6,7,9-18
Cancelled:	
New:	19-23
Pending:	1-23
Allowed:	

The claim fee status is as follows:

☐ Large Entity
☒ Small Entity

		After Amdmt	Paid for	Fee due for	Fee code
	Independent Claims:	5	4	1	Lg =102 Sm =202
	Total Claims	23	20	3	Lg =103 Sm =203

It is believed that entry of this Amendment will require payment of additional claim fees.

The claims have been amended to more clearly define the invention. Support for the amendments is either apparent or is as described below. Support for pharmaceutical compositions can be found, for example, at page 26, line 29 through page 30. line 32.

Claim Rejections - 35 U.S.C. §112, Second Paragraph

Claims 1-18 stood rejected under 35 U.S.C. §112, second paragraph, based on an assertion that certain terms in the claims rendered the claims insufficient to particularly point out and distinctly claim the subject matter that the applicant regards as the invention.

In particular, claim 1, 9, 10 and 18 have been amended to more particularly and distinctly define the subject matter of the invention. The objected to phrase "can be" has been deleted.

Claim 6 and 14 have been amended to specifically recite the "R^1" group.

Claim 7 has been amended to insert the omitted chemical radical "Z".

Dependent claims 11-17 have been amended to recite their correct dependency.

In light of the above amendments, reconsideration and withdrawal of the rejection of the claims under §112, second paragraph is respectfully requested.

Claim Rejections - 35 U.S.C. §102(b)

Claims 1-9 stood rejected under 35 U.S.C. §102(b) as anticipated by Littman et al. and Washabaugh et al.

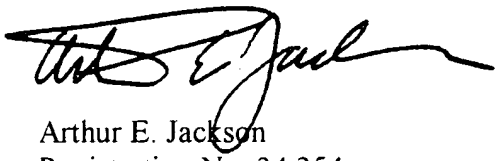
Without conceding the validity of the rejection, solely to expedite prosecution, Applicants have elected to amend claims 1 and 9. Reconsideration and withdrawal of the rejection is respectfully requested.

Applicants have provided herewith a copy of the entire Littman et al. reference whose abstract was cited by the Examiner. Applicants submit that the entire reference and not just the abstract should be of record.

Conclusion

Applicants thank the Examiner for the Office Action and believe this response to constitute a full and complete response to such Office Action. The Notice of Allowance is earnestly solicited.[2]

Respectfully submitted,



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[2] **FEE DEFICIENCY**

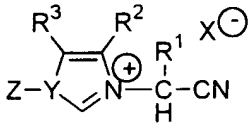
IF ANY ADDITIONAL EXTENSION IS REQUIRED, PLEASE CONSIDER THIS PAPER A PETITION FOR SUCH AN EXTENSION. ANY FEE FOR THE EXTENSION REQUIRED FOR CONSIDERATION OF THIS PAPER BUT NOT ENUMERATED ABOVE OR IN A TRANSMITTAL OR OTHER ASSOCIATED PAPER CAN BE CHARGED TO ACCOUNT NO. 04-0480.

AND/OR

IF ANY ADDITIONAL FEE IS REQUIRED FOR CONSIDERATION OF THIS PAPER, PLEASE CHARGE ACCOUNT NO. 04-0480.

APPENDIX A1: Version with Markings to Show Changes Made

1. (Amended) A compound of the formula:



wherein :

Y is N ~~or S~~;

~~Z is absent when Y is S and, if present,~~ Z is an alkyl group of 1 to 7 carbon atoms, vinyl, allyl, arylcarbonyl, amino or alkoxycarbonylalkyl, or Z is according to the formula $-CH(R^4)(CN)$, or Z is $-CH_2C(=O)R^5$, where R^5 is (a) a C_6-C_{10} aryl group, said aryl group optionally substituted by one or more alkyl, alkoxy, halo, dialkylamino, hydroxy, nitro or C_1-C_2 alkylenedioxy groups or (b) heterocyclic group containing 4-10 ring members and 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur wherein the heterocyclic group is optionally ~~can be~~ substituted by one or more substituents selected from the group consisting of alkyl, oxo, alkoxycarbonylalkyl, aryl, and aralkyl group, and the one or more substituents are optionally ~~can be~~ substituted by one or more alkyl or alkoxy groups,

R^1 and R^4 are independently hydrogen, alkyl or phenyl optionally substituted with one or more halogen, alkyl, di(lower alkyl)amino or alkoxy groups; and

R^2 and R^3 are:

1. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, allyl, amino, ω-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl,

APPENDIX A1: Version with Markings to Show Changes Made– (continued)

alkylsulfinyl, alkylthio, trifluoromethyl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, 4-[C_6 or C_{10}]arylpiperazin-1-yl, Ar {wherein, consistent with the rules of aromaticity, Ar is C_6 or C_{10} aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring is optionally ~~can be~~ fused to a benzene, pyridine, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar–alkyl, Ar-O, $ArSO_2$-, ArSO-, ArS-, $ArSO_2NH$-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-, or together R_1 and R_2 comprise methylenedioxy; or

2. together with their ring carbons form a C_6- or C_{10}- aromatic fused ring system; or
3. together with their ring carbons form a C_5-C_7 fused cycloalkyl ring having up to two double bonds including the fused double bond of the –olium or –onium containing ring, which cycloalkyl ring is optionally ~~can be~~ substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo substituents; or
4. together with their ring carbons form a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring is ~~may be~~ optionally substituted with one or more 1-pyrrolidinyl-, 4-[C_6 or C_{10}]arylpiperazin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C_1-C_3)alkylenedioxy groups; or

APPENDIX A1: Version with Markings to Show Changes Made– (continued)

5. together with their ring carbons form a five to eight membered heterocycle, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, and $S(O)_n$, where n=0,1, or 2; and

X^- is a biologically or pharmaceutically acceptable anion,

wherein aryl or Ar is optionally ~~can be~~ substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, $(C_1$-$C_3)$alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω-alkylenesulfonic acid, alkylthio, allyl, amino, ArC(O)-, ArC(O)NH-, ArO-, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, $(C_2$-$C_6)$hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl-, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, and piperidin-1-yl; and

wherein heterocycles, except those of Ar, are optionally ~~can be~~ substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, ArC(O)-, ArO-, Ar-, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl.

2. The compound of claim 1, wherein R^2 and R^3 are independently hydrogen, alkyl, or together form an alkylene bridge of 3-4 carbon atoms.

3. The compound of claim 1, wherein R^1 is hydrogen.

4. The compound of claim 1, wherein Z is an alkyl group of 1 to 7 carbon atoms.

APPENDIX A1: Version with Markings to Show Changes Made– (continued)

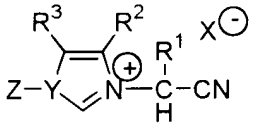
5. The compound of claim 3, wherein Z is C_1 to C_3 alkyl.

6. (Amended) The compound of claim 4, wherein $\underline{R^1}$ ~~R~~ is hydrogen.

7. (Amended) The compound of claim 1, wherein $\underline{Z}$ is an alkyl group of 1 to 7 carbon atoms, arylcarbonyl, amino or alkoxycarbonylalkyl, or Z is according to the formula -$CH(R^4)(CN)$, or Z is -$CH_2C(=O)R^5$, where R^5 is a C_6-C_{10} aryl group, said aryl group optionally substituted by one or more alkyl, alkoxy, halo, dialkylamino, hydroxy, nitro or C_1-C_2 alkylenedioxy groups.

8. The compound of claim 1, wherein Z is an alkyl group of 1 to 7 carbon atoms, arylcarbonyl, amino or alkoxycarbonylalkyl, or Z is according to the formula -$CH(R^4)(CN)$.

9. (Amended) A compound of the formula:



wherein :

Y is N ~~or S~~;

~~Z is absent when Y is S and, if present,~~ Z is an alkyl group of 1 to 7 carbon atoms, arylcarbonyl, amino or (lower)alkoxycarbonyl(lower)alkyl, or Z is according to the formula -$CH(R^4)(CN)$, or Z is -$CH_2C(=O)R^5$, where R^5 is (a) a C_6-C_{10} aryl group, said aryl group optionally substituted by one or more lower alkyl, lower alkoxy, halo, di(lower)alkylamino, hydroxy, nitro or C_1-C_2 alkylenedioxy groups

APPENDIX A1: Version with Markings to Show Changes Made– (continued)

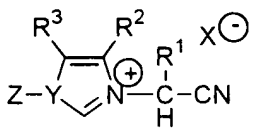
or (b) heterocyclic group containing 4-10 ring members and 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur wherein the heterocyclic group is optionally ~~can be~~ substituted by one or more substituents selected from the group consisting of alkyl, oxo, alkoxycarbonylalkyl, aryl, and aralkyl group, and the one or more substituents are optionally ~~can be~~ substituted by one or more alkyl or alkoxy groups,

R^1 and R^4 are independently hydrogen, lower alkyl or phenyl optionally substituted with one or more halogen, lower alkyl, di(lower alkyl)amino or alkoxy groups;

R^2 and R^3 are independently hydrogen, lower alkyl, or together form an alkylene bridge of 3-4 carbon atoms; and

X^- is a biologically or pharmaceutically acceptable anion.

10. (Amended) A method of, in an animal, (i) improving the elasticity or reducing wrinkles of a skin, treating (ii) diabetes or treating, inhibiting the (iii) discoloration of teeth, or ameliorating one or more of the following conditions: (iv) adverse sequelae of diabetes, (v) kidney damage, (vi) damage to blood vasculature, (vii) hypertension, (viii) retinopathy, (ix) damage to lens proteins, (x) cataracts, (xi) peripheral neuropathy, (xii) osteoarthritis, or (xiii) damage to cardiovascular tissue due to heart failure, (xiv) improving myocardial elasticity, (xv) preventing damage to tissues in the intraperitoneal cavity caused by contact with elevated levels of reducing sugars, or (xvi) treating or ameliorating one of the conditions described above, the method comprising administering an effective amount of one or more compounds of the formula:



APPENDIX A1: Version with Markings to Show Changes Made– (continued)

wherein :

Y is N or S;

Z is absent when Y is S and, if present, Z is an alkyl group of 1 to 7 carbon atoms, vinyl, allyl, arylcarbonyl, amino or alkoxycarbonylalkyl, or Z is according to the formula $-CH(R^4)(CN)$, or Z is $-CH_2C(=O)R^5$, where R^5 is (a) a C_6-C_{10} aryl group, said aryl group optionally substituted by one or more alkyl, alkoxy, halo, dialkylamino, hydroxy, nitro or C_1-C_2 alkylenedioxy groups or (b) heterocyclic group containing 4-10 ring members and 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur wherein the heterocyclic group is optionally ~~can be~~ substituted by one or more substituents selected from the group consisting of alkyl, oxo, alkoxycarbonylalkyl, aryl, and aralkyl group, and the one or more substituents are optionally ~~can be~~ substituted by one or more alkyl or alkoxy groups,

R^1 and R^4 are independently hydrogen, alkyl or phenyl optionally substituted with one or more halogen, alkyl, di(lower alkyl)amino or alkoxy groups; and

R^2 and R^3 are:

1. independently selected from hydrogen, acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, allyl, amino, ω-alkylenesulfonic acid, carbamoyl, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, alkylsulfonyl, alkylsulfinyl, alkylthio, trifluoromethyl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, 4-[C_6 or C_{10}]arylpiperazin-1-yl, Ar {wherein, consistent with the rules of aromaticity, Ar is C_6 or C_{10} aryl or a 5- or 6-membered heteroaryl ring, wherein 6-membered heteroaryl ring contains one to three

APPENDIX A1: Version with Markings to Show Changes Made– (continued)

atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring is optionally ~~can be~~ fused to a benzene, pyridine, pyrimidine, pyridazine, pyrazine, or (1,2,3)triazine (wherein the ring fusion is at a carbon-carbon double bond of Ar)}, Ar–alkyl, Ar-O, $ArSO_2$-, ArSO-, ArS-, $ArSO_2NH$-, ArNH, (N-Ar)(N-alkyl)N-, ArC(O)-, ArC(O)NH-, ArNH-C(O)-, and (N-Ar)(N-alkyl)N-C(O)-, or together R_1 and R_2 comprise methylenedioxy; or

2. together with their ring carbons form a C_6- or C_{10}- aromatic fused ring system; or

3. together with their ring carbons form a C_5-C_7 fused cycloalkyl ring having up to two double bonds including the fused double bond of the –olium or –onium containing ring, which cycloalkyl ring is optionally ~~can be~~ substituted by one or more of the group consisting of alkyl, alkoxycarbonyl, amino, aminocarbonyl, carboxy, fluoro, or oxo substituents; or

4. together with their ring carbons form a 5- or 6-membered heteroaryl ring, wherein the 6-membered heteroaryl ring contains one to three atoms of N, and the 5-membered heteroaryl ring contains from one to three atoms of N or one atom of O or S and zero to two atoms of N, each heteroaryl ring is ~~may be~~ optionally substituted with one or more 1-pyrrolidinyl-, 4-[C_6 or C_{10}]arylpiperazin-1-yl, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, piperidin-1-yl, halo or (C_1-C_3)alkylenedioxy groups; or

5. together with their ring carbons form a five to eight membered heterocycle, wherein the heterocycle consists of ring atoms selected from the group consisting of carbon, nitrogen, and $S(O)_n$, where n=0,1, or 2; and

X^- is a biologically or pharmaceutically acceptable anion,

APPENDIX A1: Version with Markings to Show Changes Made– (continued)

wherein aryl or Ar is optionally ~~can be~~ substituted with, in addition to any substitutions specifically noted, one or more substituents selected from the group consisting of acylamino, acyloxyalkyl, alkanoyl, alkanoylalkyl, alkenyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, (C_1-C_3)alkylenedioxy, alkylsulfonyl, alkylsulfinyl, ω-alkylenesulfonic acid, alkylthio, allyl, amino, ArC(O)-, ArC(O)NH-, ArO-, Ar-, Ar-alkyl-, carboxy, carboxyalkyl, cycloalkyl, dialkylamino, halo, trifluoromethyl, hydroxy, (C_2-C_6)hydroxyalkyl, mercapto, nitro, sulfamoyl, sulfonic acid, 1-pyrrolidinyl, 4-[C_6 or C_{10}]arylpiperazin-1-yl-, 4-[C_6 or C_{10}]arylpiperidin-1-yl, azetidin-1-yl, morpholin-4-yl, thiomorpholin-4-yl, and piperidin-1-yl; and

wherein heterocycles, except those of Ar, are optionally ~~can be~~ substituted with, in addition to any substitutions specifically noted, acylamino, alkanoyl, alkoxy, alkoxycarbonyl, alkoxycarbonylalkyl, alkyl, alkylamino, alkylsulfonyl, alkylsulfinyl, alkylthio, amino, ArC(O)-, ArO-, Ar-, carboxy, dialkylamino, fluoro, fluoroalkyl, difluoroalkyl, hydroxy, mercapto, sulfamoyl, or trifluoromethyl.

11. (Amended) The method of claim 10 ~~8~~, comprising administering an effective amount of one or more of the compounds wherein R^1 is hydrogen.

12 (Amended) The method of claim 10 ~~8~~, comprising administering an effective amount of one or more of the compounds wherein Z is an alkyl group of 1 to 7 carbon atoms.

13. (Amended) The method of claim 10 ~~8~~, comprising administering an effective amount of one or more of the compounds wherein Z is C_1 to C_3 alkyl.

APPENDIX A1: Version with Markings to Show Changes Made– (continued)

14. (Amended) The method of claim 12 ~~8~~, comprising administering an effective amount of one or more of the compounds wherein R^1 ~~R~~ is hydrogen.

15. (Amended) The method of claim 10 ~~11~~, comprising administering an effective amount of one or more of the compounds wherein Z is an alkyl group of 1 to 7 carbon atoms, arylcarbonyl, amino or alkoxycarbonylalkyl, or Z is according to the formula - $CH(R^4)(CN)$, or Z is $-CH_2C(=O)R^5$, where R^5 is a C_6-C_{10} aryl group, said aryl group optionally substituted by one or more alkyl, alkoxy, halo, dialkylamino, hydroxy, nitro or C_1-C_2 alkylenedioxy groups.

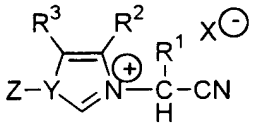
16. (Amended) The method of claim 15 ~~7~~, wherein Z is an alkyl group of 1 to 7 carbon atoms, arylcarbonyl, amino or alkoxycarbonylalkyl, or Z is according to the formula - $CH(R^4)(CN)$.

17. (Amended) The method of claim 10 ~~7~~, comprising administering an effective amount of the one or more compounds to improve myocardial elasticity or reduce any loss of myocardial elasticity in heart failure.

18. (Amended) A method of, in an animal, (i) improving the elasticity or reducing wrinkles of a skin, treating (ii) diabetes or treating, inhibiting the (iii) discoloration of teeth, or ameliorating one or more of the following conditions: (iv) adverse sequelae of diabetes, (v) kidney damage, (vi) damage to blood vasculature, (vii) hypertension, (viii) retinopathy, (ix) damage to lens proteins, (x) cataracts, (xi) peripheral neuropathy, (xii) osteoarthritis, or (xiii) damage to cardiovascular tissue due to heart failure, (xiv) improving myocardial elasticity, (xv) preventing damage to tissues in the intraperitoneal

APPENDIX A1: Version with Markings to Show Changes Made– (continued)

cavity caused by contact with elevated levels of reducing sugars, or (xvi) treating or ameliorating one of the conditions described above, the method comprising administering an effective amount of one or more compounds of the formula:



wherein:

Y is N or S;

Z is absent when Y is S and, if present, Z is an alkyl group of 1 to 7 carbon atoms, arylcarbonyl, amino or (lower)alkoxycarbonyl(lower)alkyl, or Z is according to the formula $-CH(R^4)(CN)$, or Z is $-CH_2C(=O)R^5$, where R^5 is (a) a C_6-C_{10} aryl group, said aryl group optionally substituted by one or more lower alkyl, lower alkoxy, halo, di(lower)alkylamino, hydroxy, nitro or C_1-C_2 alkylenedioxy groups or (b) heterocyclic group containing 4-10 ring members and 1-3 heteroatoms selected from the group consisting of oxygen, nitrogen and sulfur wherein the heterocyclic group <u>is optionally</u> ~~can be~~ substituted by one or more substituents selected from the group consisting of alkyl, oxo, alkoxycarbonylalkyl, aryl, and aralkyl group, and the one or more substituents <u>is optionally</u> ~~can be~~ substituted by one or more alkyl or alkoxy groups,

R^1 and R^4 are independently hydrogen, lower alkyl or phenyl optionally substituted with one or more halogen, lower alkyl, di(lower alkyl)amino or alkoxy groups;

R^2 and R^3 are independently hydrogen, lower alkyl, or together form an alkylene bridge of 3-4 carbon atoms; and

X^- is a biologically or pharmaceutically acceptable anion.